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Clopidogrel 600-Mg Double Loading Dose Achieves Stronger Platelet Inhibition Than Conventional Regimens

Results From the PREPAIR Randomized Study

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Objectives The objective of this study was to compare the level of platelet inhibition achieved by 3 different clopidogrel loading regimens in patients undergoing elective angiography and percutaneous coronary intervention when appropriate.

Background Optimal platelet inhibition is a key therapeutic goal for patients undergoing percutaneous coronary intervention. Although 600 mg has been described as the maximum absorbed dose when given as a single bolus, the effects of 2 boluses given 24 h apart have not been described.

Methods Patients (n = 148) were randomly assigned to one of 3 regimens: Group A, clopidogrel 300 mg the day before (≥15 h) + 75 mg the morning of the procedure; Group B, clopidogrel 600 mg the morning of the procedure (≥2 h); and Group C, clopidogrel 600 mg the day before (≥15 h) and 600 mg the morning of the procedure (≥2 h). Blood samples were obtained at baseline and immediately before angiography. Peak and late platelet aggregation were measured in platelet rich plasma, with researchers blinded to treatment allocation.

Results There was a consistent difference favoring Group C in all aggregation parameters. Percent inhibition in Groups A, B, and C was 31.4%, 29.0%, and 49.5%, respectively, for peak aggregation (5 μmol/l adenosine diphosphate; $p < 0.0001$) and 54.1%, 57.7%, and 81.1%, respectively, for late aggregation ($p < 0.0001$). Similar striking reductions were observed when 20 μmol/l adenosine diphosphate was used. All comparisons between Group C and the other 2 groups were statistically significant, and those between Groups A and B were not.

Conclusions Clopidogrel 600-mg double bolus achieves greater platelet inhibition than conventional single loading doses. (J Am Coll Cardiol 2008;51:1066–72) © 2008 by the American College of Cardiology Foundation

Optimal platelet inhibition is a key therapeutic goal for patients undergoing percutaneous coronary intervention (PCI). The combination of aspirin plus clopidogrel currently represents the standard of care in this setting (1–3). Clopidogrel loading affords more rapid and more potent platelet aggregation inhibition than the chronically administered dose (4). This better inhibition leads to clinical benefits in the context of PCI (5,6) and is therefore currently recommended before interventions (1–3,7,8). Single loading doses up to 900 mg before PCI have failed to show significantly greater platelet inhibition than the 600 mg loading dose (7,8). This limitation may be due to limited clopidogrel absorption (8), but time-dependent, cumulative efficacy also has been suggested (9). Clopidogrel loading doses of 600 mg at least 2 h before and 300 mg given at least 15 h before catheterization have been independently proposed as optimal dosages but have not been directly compared. In addition, the effects of 2 separate loading doses of 600 mg, given 18 to 24 h apart, have not been described. Therefore, the optimal clopidogrel loading dose remains unknown. The main objective of this randomized study was to compare the degree of platelet inhibition achieved by 3 different clopidogrel loading regimens, including a double 600-mg loading dose in patients undergoing elective angiography and PCI when appropriate. Our hypothesis was

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that a larger loading dose and optimal treatment duration would accelerate and potentiate the antiaggregatory effects of clopidogrel.

Methods

Patient population. The protocol was approved by the institutional ethics committee, and patients gave written informed consent. Patients with suspected or documented coronary artery disease admitted to our hospital for elective coronary angiography and PCI when appropriate were considered eligible. Patients with unstable angina, acute or recent (<14 days) myocardial infarction; who were receiving glycoprotein IIb/IIIa inhibitors; suffered a stroke within 3 months; exhibited malignancies, active bleeding, or bleeding diathesis; underwent oral anticoagulation with a coumarin derivate or prothrombin time >1.5 times control; had recent treatment (<30 days) with a GP IIb/IIIa antagonist or thienopyridine; a platelet count <100,000/mm3; a serum creatinine >180 mmol/l; with severe liver disease resulting in abnormal bilirubin levels; with a known allergic reaction to thienopyridines (clopidogrel or ticlopidine); or had concomitant investigational drug use within 1 month were excluded.

Study design. Patients were randomly assigned to 1 of 3 loading dose regimens according to an automated randomization list (1:1:1 ratio) provided by the Montreal Heart Institute Coordinating Center (Montreal, Canada) in sealed envelopes: Group A, clopidogrel 300 mg the day before (≥15 h) + 75 mg the morning of the interventional procedure; Group B, clopidogrel 600 mg the morning of (≥2 h before) the interventional procedure; and Group C, clopidogrel 600 mg the day before (≥15 h) and 600 mg the morning of (≥2 h before) the interventional procedure. Clopidogrel loading doses were administered in an open label fashion by research nurses, but technicians performing aggregation studies remained completely blinded to group assignment and did not have any direct contact with patients. All stented patients received 75 mg of clopidogrel daily for at least 30 days as clinically indicated after implantation. Blood was collected at the time of randomization (baseline), immediately before coronary angiography, and the next morning (12 to 24 h) when a PCI was performed (post-PCI). All patients were examined for complications before hospital discharge and contacted by telephone at 1 month to assess for adverse events. Diagnostic and interventional procedures were performed according to standard clinical practice.

Aggregometry. Blood was collected from the forearm into 2 4.5-ml Vacutainer tubes containing 0.5 ml of sodium citrate 3.2% (Becton Dickinson, Mississauga, Ontario, Canada). Platelet counts were measured with a Hematology system ADVIA60 (Bayer Inc., Toronto, Ontario, Canada). Platelet-rich plasma (PRP) was prepared by centrifuging blood for 10 min at 130 *g*. The remaining blood was further centrifuged for 15 min at 1,800 *g* to prepare platelet-poor plasma (PPP). Platelet-rich plasma was adjusted to platelet counts of 250,000 platelets/μl by adding PPP as needed. Platelet aggregation was performed in stirred (135 *g*) diluted PRP using a light transmission aggregometer (Model 570VS, Chrono-Log Corporation, Havertown, Pennsylvania). The PRP was used to set 0 light transmission and PPP to set 100 light transmission. Platelet aggregation was systematically measured after the addition of ADP at concentrations of 5 and 20 μmol/l (Sigma Chemical Co., Oakville, Ontario, Canada). Peak aggregation (Agg_{peak}) was measured at 1 to 2 min after the addition of the agonist, and late aggregation (Agg_{6min}) was measured at 6 min, accounting then for disaggregation (10). Percent inhibition of platelet aggregation was calculated as follows: (intensity of aggregation on treatment − intensity of aggregation at baseline)/(intensity of aggregation at baseline).

Abbreviations and Acronyms

ADP = adenosine diphosphate
Agg_{peak} = peak aggregation
Agg_{6min} = late aggregation
PCI = percutaneous coronary intervention
PPP = platelet-poor plasma
PRP = platelet-rich plasma

End points. The primary end point of the study was the percent inhibition of Agg_{peak} at the time of angiography. Secondary end points included the percent inhibition of Agg_{6min}; the percent inhibition of Agg_{peak} post-PCI; the prevalence of nonresponders (resistance) to clopidogrel using 3 definitions (<10%, <20%, and <40% decrease in Agg_{peak}, respectively) (11–14); the occurrence of death, myocardial infarction, or target vessel revascularization up to 30 days after procedure; and the occurrence of any of the following vascular or hemorrhagic complications: 1) major bleeding (defined as intracranial or clinically relevant bleeding associated with a decrease in hemoglobin of >5 g/dl); 2) minor bleeding (clinically overt hemorrhage associated with a fall in hemoglobin ≤5 g/dl); 3) access-site complications (hematoma, pseudoaneurysm, or arteriovenous fistula); and 4) thrombocytopenia with platelet count <70,000/mm^3 or side effect requiring interruption of clopidogrel.

Sample size calculation and statistical analysis. The primary assumption was that Group C regimen (600-mg double loading dose) would increase inhibition of platelet aggregation by at least 15% over that of Groups A and B. The study had 80% power to evaluate this difference in the primary end point with an alpha-level of 0.05 and 50 patients in each group, assuming a standard deviation of 25%. Continuous variables are expressed as mean ± SD, and their differences were tested with a one-way analysis of variance. Categorical variables are expressed as frequencies and percentage; the chi-square test was used unless otherwise indicated. The Fisher exact test was used when the row total was <10. A 1-way analysis of variance was used to compare the inhibition of platelet aggregation among the 3 groups. All pairwise comparisons were performed only if the global F test was significant at the 0.05 level. No adjustments were made to control for the

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family-wise error rate. A repeated measure analysis of covariance model, including baseline value, time (baseline, angiography, post-PCI), group (Group A, Group B, Group C), and the interaction term (time*group), was performed to determine the post-PCI inhibition of Agg_{peak}. If the interaction term was significant at the 0.05 level, then comparisons between groups at each time point were done. To quantify the changes between the time points, estimates were calculated to compare the groups on the absolute changes between the 3 time points. The changes between the time points are represented as percentages for clinical interpretation although the p values are calculated from the absolute changes. All analyses were done with SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and conducted at the 0.05 significance level.

Results

Patient characteristics. The baseline characteristics of patients were well matched in the 3 study groups, except for diabetes which was more frequent in Groups A and B (Table 1). Adjusting statistically for diabetes did not alter any of the results.

Main outcome. Percent inhibition of Agg_{peak} at the time of angiography when platelets were stimulated with 5 or 20 μmol/l ADP is illustrated in Figure 1. Inhibition of platelet aggregation was consistently better in the clopidogrel 600 mg double bolus group as compared with the other 2 regimens. Percent inhibition of Agg_{peak} was 31.4% in Group A, 29.0% in Group B, and 49.5% in Group C ($p < 0.0001$) when platelets were stimulated with 5 μmol/l ADP and 22.4%, 22.3%, and 39.8%, respectively, with 20 μmol/l ADP ($p < 0.0001$). The Agg_{peak} values did not differ at baseline ($p = 0.29$ with 5 μmol/l ADP and $p = 0.24$ with 20 μmol/l ADP) but were significantly different on treatment ($p < 0.0001$ with both 5 and 20 μmol/l ADP) (Table 2). Comparisons between Group C and other groups were highly significant ($p = 0.0002$ vs. Group A, $p < 0.0001$ vs. Group B), and those between Groups A and B were not ($p = 0.62$).

Secondary outcomes. Percent inhibition of Agg_{6min} results are illustrated in Figure 2. Late platelet aggregation inhibition was also consistently stronger in the clopidogrel 600 mg double bolus group as compared with the other 2 regimens. Percent inhibition of Agg_{6min} was

Table 1 Baseline Demographics

	Group A (n = 49)	Group B (n = 49)	Group C (n = 50)
Age, mean (SD), yrs	61.8 (8.9)	61.9 (8.9)	61.3 (9.7)
Weight, mean (SD), kg	83.4 (18.7)	85.1 (16.0)	83.6 (17.5)
Height, mean (SD), cm	166.3 (6.9)	166.9 (8.3)	166.5 (8.6)
Male, n (%)	41 (83.7)	39 (79.6)	35 (70.0)
Risk factors, n (%)			
Hypercholesterolemia	43 (87.8)	41 (83.7)	38 (76.0)
Hypertension	38 (77.6)	36 (73.5)	32 (64.0)
Current smoker	15 (30.6)	9 (18.4)	11 (22.0)
Diabetes	15 (30.6)	16 (33.3)	6 (12.2)
Family history of CAD	33 (67.4)	30 (61.2)	35 (70.0)
History, n (%)			
Myocardial infarction	15 (31.3)	14 (29.2)	7 (14.0)
Coronary angioplasty	8 (16.7)	11 (22.5)	12 (24.5)
Coronary bypass	7 (14.3)	4 (8.2)	3 (6.0)
Procedure, n (%)			
PCI	12 (25.5)	13 (27.1)	15 (30.0)
Radial access	28 (59.6)	31 (66.0)	28 (56.0)
Number of coronary vessels diseased, n (%)			
0-vessel disease	10 (20.4)	12 (24.5)	15 (30.0)
1-vessel disease	12 (24.5)	9 (18.4)	8 (16.0)
2-vessel disease	10 (20.4)	11 (22.5)	16 (32.0)
3-vessel disease	17 (34.7)	17 (34.7)	11 (22.0)
Left ventricular ejection fraction, mean (SD)	61.2% (9.1)	61.0% (8.8)	61.8% (5.3)
Medications, n (%)			
Aspirin*	48 (98.0)	47 (95.9)	49 (98.0)
Statin	37 (78.7)	42 (87.5)	39 (78.0)
Beta-blocker	34 (72.3)	26 (54.2)	27 (54.0)
ACEI/ARA	30 (63.8)	24 (50.0)	23 (46.0)
Calcium blocker	19 (40.4)	20 (41.7)	16 (32.0)
Creatinine, mean (SD) $\mu mol \cdot ml^{-1}$	95 (23)	91 (22)	91 (15)

*Fisher exact test was used to test nonsignificance.
ACEI = angiotensin-converting enzyme inhibitor; ARA = angiotensin receptor agonist; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

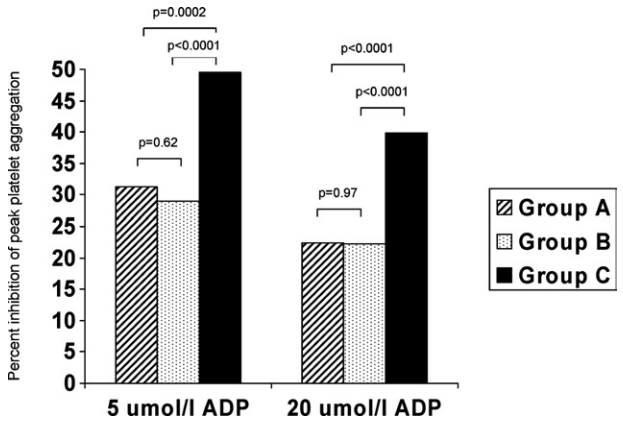

Figure 1 Percent Inhibition of Peak Aggregation

Group A, clopidogrel 300 mg the day before (≥15 h) + 75 mg the morning of the interventional procedure; Group B, clopidogrel 600 mg the morning of (≥2 h before) the interventional procedure; Group C, clopidogrel 600 mg the day before (≥15 h) and 600 mg the morning of (≥2 h before) the interventional procedure. Significant differences between Groups A versus C and Groups B versus C were found for 5 μmol/l and 20 μmol/l adenosine diphosphate (ADP) (see text for details).

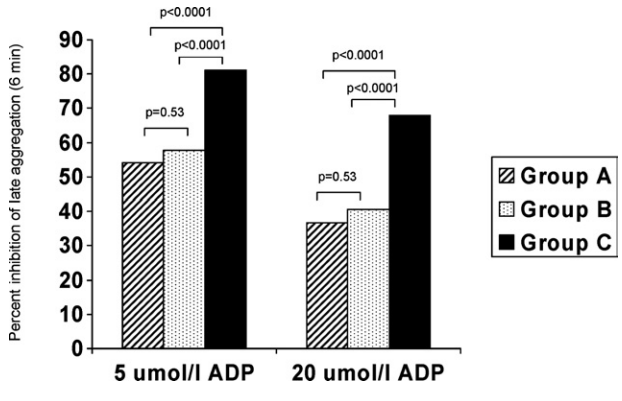

Figure 2 Percent Inhibition of Late Aggregation

Late platelet aggregation: 6 min after the addition of the agonist. Group A, clopidogrel 300 mg the day before (≥15 h) + 75 mg the morning of the interventional procedure; Group B, clopidogrel 600 mg the morning of (≥2 h before) the interventional procedure; Group C, clopidogrel 600 mg the day before (≥15 h) and 600 mg the morning of (≥2 h before) the interventional procedure. Significant differences between Groups A versus C and Groups B versus C were found for both for 5 and 20 μmol/l adenosine diphosphate (ADP) (see text for details).

54.1% in Group A, 57.7% in Group B, and 81.1% in Group C when platelets were stimulated with 5 μmol/l ADP ($p < 0.0001$) and 36.7%, 40.5%, and 68.0%, respectively, with 20 μmol/l ADP ($p < 0.0001$). Agg_{6min} values did not differ at baseline ($p = 0.09$ with 5 μmol/l ADP and $p = 0.12$ with 20 μmol/l ADP) but were significantly different on treatment ($p < 0.0001$) (Table 3). Comparisons between Group C and other groups were highly significant ($p < 0.0001$ vs. Group A, $p < 0.0001$ vs. Group B), and those between groups, A and B were not ($p \geq 0.50$). The more potent platelet inhibition observed at the time of angiography in Group C was maintained after PCI ($n = 36$). Percent inhibition of post-PCI Agg_{peak} (20 μmol/l ADP) was 21.0% in Group A, 28.4% in Group B, and 59.8% in Group C ($p < 0.0001$ Group C vs. A; $p = 0.0005$ Group C vs. B; $p = 0.25$ Group A vs. B).

Interestingly, there were no nonresponders to clopidogrel in Group C as compared with the other groups using <10% decrease in Agg_{peak} in response to 5 μmol/l ADP (9 in Group A, 8 in Group B and 0 in Group C, $p = 0.005$). When using <20% or <40% decrease as alternative definitions for nonresponsiveness, there remained a highly significant advantage of the double bolus regimen (Group C) as compared with the other 2 groups ($p = 0.001$ and $p = 0.0002$, respectively) (Fig. 3A). Similarly striking results were seen when 20 μmol/l ADP was used (Fig. 3B).

Safety. There was no death, rehospitalization for myocardial infarction, or repeat target vessel revascularization up to 30 days. Post-PCI cardiac troponin T elevations ≥0.1 μg/l were infrequent and equally distributed (2 [22%] in Group A, 2 [18%] in Group B and 3 [21%] in Group C, Fisher exact $p = 1.0$). There was no episode of major bleeding during 1 month follow-up. The incidence of minor bleeding was low and similar in the 3 groups, although numerically more frequent in Group B (3 in Group A, 8 in Group B, and 4 in Group C, $p = 0.19$) and mainly related to puncture sites (e.g., ecchymosis, oozing, hematoma). Clopidogrel up

Table 2 Peak Aggregation Values

	Group A	Group B	Group C	p Value
5 μmol/l ADP				
Baseline (SD)	61.0 (11.6)	57.8 (10.4)	58.3 (9.1)	0.29
Pre-angiography (SD)	41.3 (14.8)	39.7 (11.7)	29.6 (12.4)*	<0.0001†
20 μmol/l ADP				
Baseline (SD)	72.2 (8.5)	70.8 (7.1)	69.3 (8.7)	0.24
Pre-angiography (SD)	55.5 (14.6)	54.7 (13.5)	41.6 (14.9)‡	<0.0001†

*$p = 0.0002$ for Group C versus A; $p < 0.0001$ for Group C versus B; $p = 0.62$ for Group B versus A. †p value is from a 1-way analysis of covariance adjusted for baseline. ‡$p < 0.0001$ for Group C versus A; $p < 0.0001$ for Group C versus B; $p = 0.97$ for Group B versus A.
ADP = adenosine diphosphate.

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Table 3 Late Aggregation Values (6 Min)

	Group A	Group B	Group C	p Value
5 μmol/l ADP				
Baseline	55.4 (14.7)	51.2 (13.0)	49.1 (13.9)	0.09
Pre-angiography	25.2 (16.0)	20.8 (14.5)	10.4 (13.8)*	<0.0001†
20 μmol/l ADP				
Baseline	70.8 (9.0)	69.3 (7.5)	67.0 (9.9)	0.12
Pre-angiography	44.5 (19.5)	41.1 (20.3)	22.1 (20.4)‡	<0.0001†

*$p < 0.0001$ for Group C versus A; $p < 0.0001$ for Group C versus B; $p = 0.53$ for Group B versus A. †p value is from a 1-way analysis of covariance adjusted for baseline. ‡$p < 0.0001$ for Group C versus A; $p < 0.0001$ for Group C versus B; $p = 0.53$ for Group B versus A.
ADP = adenosine diphosphate.

to 600 mg twice within 18 to 24 h was otherwise well tolerated. No patient developed clinically evident allergy to clopidogrel.

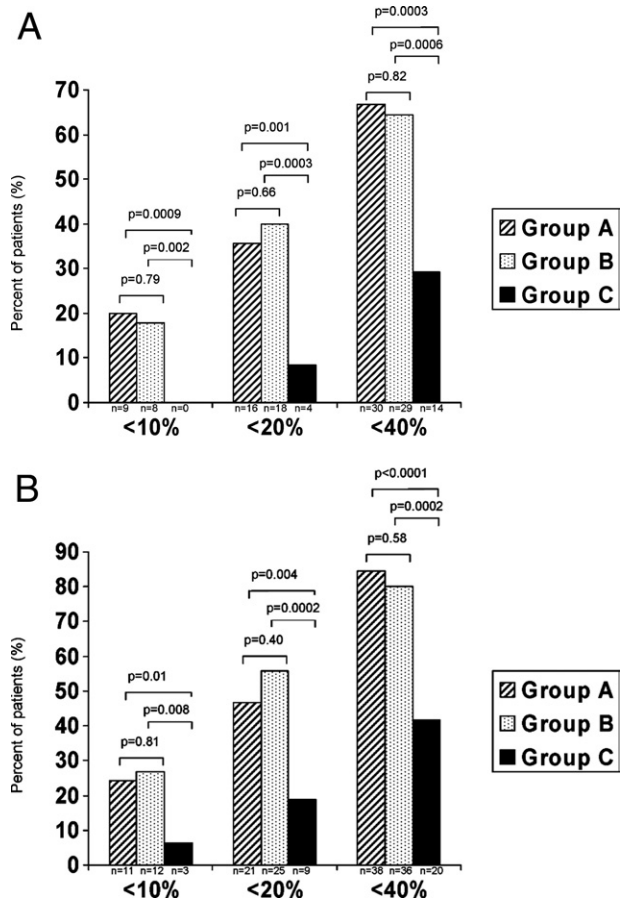

Figure 3 Clopidogrel Resistance

Data presented according to 3 definitions of resistance: <10%, <20%, and <40% decrease in peak platelet aggregation. **(A)** 5 μmol/l ADP; **(B)** 20 μmol/l ADP. Group A, clopidogrel 300 mg the day before (≥15 h) + 75 mg the morning of the interventional procedure; Group B, clopidogrel 600 mg the morning of (≥2 h before) the interventional procedure; Group C, clopidogrel 600 mg the day before (≥15 h) and 600 mg the morning of (≥2 h before) the interventional procedure. Significant differences between Groups A versus C and Groups B versus C were found for 5 μmol/l and 20 μmol/l adenosine diphosphate (see text for details).

Discussion

To our knowledge, this is the largest study to date comparing clopidogrel loading regimens and the first to report the effects of a double bolus loading strategy before an interventional procedure. Although other studies have compared increasing loading doses (up to 900 mg) given as single boluses only (7,8), the present study was specifically designed to integrate the concepts of larger doses to accelerate and potentiate the antiaggregratory effects of clopidogrel and optimal treatment duration to benefit from time-dependent, cumulative effects. The most striking finding in this study is that a double bolus of 600 mg of clopidogrel achieves more potent platelet inhibition than either clopidogrel 600-mg single bolus or 300-mg single bolus ≥15 h before plus 75 mg the morning of an interventional procedure. Another important finding is that clopidogrel 300-mg single bolus given ≥15 h before plus 75 mg the morning of an interventional procedure provides equivalent platelet inhibition as a larger 600-mg single bolus given the morning of the procedure (≥2 h).

The most likely explanation for the better platelet inhibition achieved with a double bolus of clopidogrel lies in the higher plasma concentrations of clopidogrel and its active metabolite. von Beckerath et al. (8) have demonstrated that loading with a single bolus of clopidogrel 600 mg resulted in greater plasma concentrations of the active metabolite of clopidogrel as compared with loading with a single bolus of 300 mg. In the same study, loading with clopidogrel 900-mg single bolus failed to increase further the plasma concentrations of the active metabolite of clopidogrel and its unchanged form, strongly suggesting that intestinal absorption is the limiting step when single doses exceeding 600 mg are administered. A strategy of 2 separate clopidogrel 600 mg doses at 18- to 24-h interval would likely circumvent this limiting step and allow more absorption of the drug. Given that clopidogrel is an inactive prodrug that requires to be metabolized to an active compound and provided that the metabolism of clopidogrel does not become saturated, the double bolus strategy can be expected to achieve better inhibition of platelet aggregation, as was the case in this study. More specifically, a greater concentration of the active metabolite could lead to a more complete saturation

of the P2Y12 receptors, which appears very partial at standard clopidogrel doses (15). In addition, if the circulating levels are high enough, it is not completely impossible that other platelet receptors be blocked concomitantly (e.g., P2Y1), further inhibiting aggregation.

Interestingly, our results highlight a time-dependent catch-up phenomenon after a 300-mg loading dose as compared with the 600-mg loading dose. Previous studies have convincingly demonstrated a more rapid and somewhat more potent inhibition of platelet aggregation when 600 mg of clopidogrel was compared with 300 mg during the first 24 h (12,16). However, these studies have not described the peak level of inhibition achieved when loading doses were administered at different intervals before intervention. Groups A and B in the current study did not differ in terms of the intensity of the inhibition of platelet aggregation at the time of the angiography despite a loading dose twice as large. The main difference between the respective regimens of both groups (in addition to the dosages) was the timing of the administration of the loading dose (>15 h vs. >2 h). It is possible that although the peak level of active clopidogrel metabolite reached after 300-mg was lower than with 600 mg, the length of exposure might have compensated if the clearance of the active metabolite is slower than previously described (8). The effect of the additional 75-mg dose the morning of the intervention might also have played a role to potentiate to the inhibitory effect of the 300-mg loading dose on the existing platelets or by inhibiting the platelets produced by the bone marrow in the interim. Therefore, a more modest loading dose given early enough (e.g., ≥15 h) could be equivalent to a larger loading dose given shortly before PCI.

The importance of nonresponsiveness (resistance) to clopidogrel may be underestimated clinically. Indeed, an increased level of inhibition in patients that would not have otherwise achieved an adequate response with standard dosing may have a larger impact than a further increase in those with an already adequate response. Many data now suggest that a poor response to clopidogrel is associated with increased event rates (13,14,17–21). Recently, Patti et al. (22) demonstrated that pretreatment with a 600-mg loading dose of clopidogrel reduced periprocedural myocardial infarctions by one-half in patients undergoing PCI when compared with a 300-mg loading dose. Buonamici et al. (23) identified nonresponsiveness to clopidogrel in vitro as a strong independent predictor of stent thrombosis in patients receiving drug-eluting stents. Furthermore, Bliden et al. (24) showed that patients undergoing nonemergent PCI who exhibit high ADP-induced platelet aggregation while being treated with clopidogrel are at increased risk for post-procedural ischemic events. The absence of nonresponders to clopidogrel when using the 600-mg double loading strategy in the present study suggests that this may represent a clinically relevant finding. Because we identified a clopidogrel loading regimen that achieves stronger platelet inhibition and decreases the proportion of nonresponders without apparently increasing bleeding, it is indeed reasonable to expect reductions in clinical events. However, larger studies are needed to confirm the clinical impact of this double loading dose. The hypothesis that stronger platelet inhibition is associated with better outcomes is now being tested with P2Y12 receptor blockers, both thienopyridines and nonthienopyridines. If this hypothesis is demonstrated efficacious and safe, the double loading dose as used in this study would become of even greater interest given the well documented efficacy of clopidogrel in large clinical trials. Until then, the double loading dose approach could be used in the large number of patients referred for coronary angiography and ad hoc PCI from other hospitals or as outpatient.

Study limitations. There are limitations to this study. First, open-label administration of clopidogrel was used. Because the primary end point was not clinical and all laboratory analyses were performed with researchers blinded to treatment assignments, no impact on the primary end point is expected. Second, the study was underpowered to detect meaningful differences in clinical events.

Conclusions

A clopidogrel 600-mg double loading dose (first dose given more than 15 h before and second dose given the morning of an interventional procedure) achieves greater platelet inhibition than conventional single loading doses. Clopidogrel administered as a 300-mg single bolus given ≥15 h prior to plus 75 mg on the morning of an intervention achieves equivalent platelet inhibition as a 600-mg single bolus loading dose given on the morning of the procedure.

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REFERENCES

1. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:e1–121.
2. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions: the task force for percutaneous coronary interventions of the European society of cardiology. Eur Heart J 2005;26:804–47.
3. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:576S–99S.
4. Helft G, Osende JI, Worthley SG, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. Arterioscler Thromb Vasc Biol 2000;20:2316–21.
5. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.

6. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
7. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non–ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. J Am Coll Cardiol 2006;48:931–8.
8. von Beckerath N, Taubert D, Pogatsa-Murray G, Schomig E, Kastrati A, Schomig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. Circulation 2005;112:2946–50.
9. Bal dit Sollier C, Mahe I, Berge N, Simoneau G, Bergmann JF, Drouet L. Reduced thrombus cohesion in an ex vivo human model of arterial thrombosis induced by clopidogrel treatment: kinetics of the effect and influence of single and double loading-dose regimens. Thromb Res 2003;111:19–27.
10. Labarthe B, Theroux P, Angioi M, Ghitescu M. Matching the evaluation of the clinical efficacy of clopidogrel to platelet function tests relevant to the biological properties of the drug. J Am Coll Cardiol 2005;46:638–45.
11. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
12. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–6.
13. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171–5.
14. Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. Catheter Cardiovasc Interv 2003;59:295–302.
15. Wong PC, Crain EJ, Watson CA, et al. Platelet aggregometry and receptor binding to predict the magnitude of antithrombotic and bleeding time effects of clopidogrel in rabbits. J Cardiovasc Pharmacol 2007;49:316–24.
16. Muller I, Seyfarth M, Rudiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–3.
17. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. J Am Coll Cardiol 2005;46:1820–6.
18. Hochholzer W, Trenk D, Bestehorn HP, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006;48:1742–50.
19. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. J Am Coll Cardiol 2005;46:1827–32.
20. Ajzenberg N, Aubry P, Huisse MG, et al. Enhanced shear-induced platelet aggregation in patients who experience subacute stent thrombosis: a case-control study. J Am Coll Cardiol 2005;45:1753–6.
21. Cuisset T, Frere C, Quilici J, et al. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non–ST-segment elevation acute coronary syndrome undergoing coronary stenting. J Am Coll Cardiol 2006;48:1339–45.
22. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention. Results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. Circulation 2005;111:2099–106.
23. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. J Am Coll Cardiol 2007;49:2312–7.
24. Bliden KP, DiChiara J, Tantry US, Bassi AK, Chaganti SK, Gurbel PA. Increased risk in patients with high platelet aggregation receiving chronic clopidogrel therapy undergoing percutaneous coronary intervention: is the current antiplatelet therapy adequate? J Am Coll Cardiol 2007;49:657–66.